IN THE CLAIMS

Please add new Claim 106 as follows:

-- 106. (new) A human 293 embryonal kidney cell wherein the genome of the cell has inserted therein, via homologous recombination, an enhancer and promoter of cytomegalovirus operatively associated with the endogenous cellular human erythropoietin gene, so that the cell expresses human erythropoietin. --

Please cancel Claims 26, 27, 32-44, 46-66, 69, 70, 73-75, 77-82, 84-88, 91, 92, 94-98, 100, and 102-104, without prejudice, and replace the cancelled claims with new Claims 107-119, as follows:

-- 107. (new) A method for large scale production of a mammalian target gene product in cell culture, comprising:

(1) culturing a mammalian continuous cell line which was prepared by the steps of:

(a) integrating, via targeted homologous recombination, a nucleotide regulatory sequence heterologous to the target gene, into the genome of a mammalian host cell, so that the integrated nucleotide regulatory sequence is operably associated with the mammalian target gene contained in the host cell genome to form a recombined mammalian target gene; and

(b) transferring the recombined mammalian target gene to a mammalian continuous cell line compatible with the integrated

nucleotide regulatory sequence, so that the mammalian target gene product is expressed by the mammalian continuous cell line in culture; and

(2) recovering the mammalian target gene product from the cell culture.

108. (new) The method of Claim 107 in which the mammalian continuous cell line further contains an amplifiable gene operatively associated with the mammalian target gene controlled by the heterologous nucleotide regulatory sequence, and the mammalian continuous cell line is cultured under conditions that amplify the amplifiable gene and the mammalian target gene, so that expression of the mammalian target gene controlled by the heterologous nucleotide regulatory sequence is enhanced, in which the mammalian continuous cell line was prepared by:

(a) integrating, via targeted homologous recombination, the amplifiable gene within an intron or proximal to the mammalian target gene contained in the mammalian host cell, so that the amplifiable gene and the heterologous regulatory sequence are operatively associated with the mammalian target gene; and

(b) transferring the recombined mammalian target gene to a mammalian continuous cell line, so that the expressed mammalian target gene controlled by the heterologous

regulatory sequence is amplified when the mammalian continuous cell line is cultured under conditions that amplify the amplifiable gene.

109. (new) A method for producing a mammalian continuous cell line used for large-scale protein production in culture, comprising:

(a) integrating, via targeted homologous recombination, a nucleotide regulatory sequence heterologous to a mammalian target gene contained in a mammalian host cell, so that the integrated nucleotide regulatory sequence is operably associated with the mammalian target gene to form a recombined mammalian target gene; and

(b) transferring the recombined mammalian target gene to a mammalian continuous cell line compatible with the integrated nucleotide regulatory sequence, so that the mammalian target gene product is expressed by the mammalian continuous cell line in culture.

110. (new) The method for producing the mammalian continuous cell line of Claim 109, which further comprises:

(a) integrating, via targeted homologous recombination, an amplifiable gene within an intron or proximal to the mammalian

target gene contained in the mammalian host cell, so that the amplifiable gene and the heterologous regulatory sequence are operably associated with the mammalian target gene; and

(b) transferring the recombined mammalian target gene to a mammalian continuous cell line, so that the expressed mammalian target gene controlled by the heterologous regulatory sequence is amplified when the mammalian continuous cell line is cultured under conditions that amplify the amplifiable gene.

111. (new) The method of Claim 107, 108, 109 or 110 in which the mammalian host cell is a human cell.

112. (new) The method of Claim 107, 108, 109 or 110 in which the mammalian host cell is a primary cell.

113. (new) The method of Claim 112 in which the primary mammalian cell is a fibroblast, lymphocyte, epithelial or endothelial cell.

114. (new) The method of Claim 107, 108, 109 or 110 in which the mammalian target gene is a human gene.

115. (new) The method of Claim 114 in which the target gene encodes an interleukin, a growth factor, a colony

stimulating factor, erythropoietin, a plasminogen activator, an enzyme, an interferon, or a receptor protein.

116. (new) The method of Claim 107, 108, 109 or 110 in which the heterologous regulatory sequence is a viral promoter or a promoter/enhancer.

117. (new) The method of Claim 116 in which the promoter/enhancer is a cytomegalovirus promoter/enhancer.

118. (new) The method of Claim 108 or 110 in which the amplifiable gene is dihydrofolate reductase, metallothionein-I, metallothionein-II, adenosine deaminase, ornithine decarboxylase, or glutamine synthetase.

119. (new) The method of Claim 107, 108, 109 or 110 in which the mammalian continuous cell line is a Chinese hamster ovary cell line, a monkey kidney cell line, a C127 mouse fibroblast cell line, a 3T3 mouse cell line, a Vero cell line or a 293 cell line. --

REMARKS

In order to reduce the issues involved in this prosecution, the claims have been redrafted to more particularly point out and distinctly claim two embodiments of the invention. In particular, Claim 105 and new Claim 106 cover mammalian host cells in which the expression of a resident endogenous target gene is activated by the integration of a regulatory sequence that controls gene